

Statement from the Work Session on Chemically-Induced Alterations in the Developing Immune System: The Wildlife/Human Connection

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The Problem

Many compounds introduced into the environment by human activity have the potential to disturb the immune system of wildlife and humans. The consequences of such interference on the developing immune system are not well understood. Because of the pervasive contamination of the environment by compounds with such activity, a multidisciplinary group of experts gathered in retreat at Wingspread, Racine, Wisconsin, 10–12 February 1995, to assess what is known about the issue. Participants included experts in the fields of biology, ecology, economy, comparative immunology, medicine, microbiology, neurobiology, toxicology, veterinary medicine, virology, wildlife biology, and zoology.

The purposes of the meeting were *a)* to reach agreement in principle on the magnitude and scope of the problem of exposure to synthetic chemicals on the immune systems of wildlife and humans, with a special emphasis on development; *b)* to identify the conclusions that can be drawn with confidence from the existing data; and *c)* to establish a research agenda that would clarify uncertainties that need to be addressed.

Consensus Statement

The following consensus was reached by participants at the workshop.

This Consensus Statement is part of the Wingspread Work Session on Chemically-induced Alterations in the Developing Immune System: The Wildlife/Human Connection held 10–12 February 1995 in Racine, Wisconsin. Manuscript received 3 October 1995; manuscript accepted 22 February 1996.

This consensus statement reflects the professional wisdom of the scientists at the work session and not necessarily the institutions or agencies in which they are employed.

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Abbreviations used: DES, diethylstilbestrol; PCBs, polychlorinated biphenyls.

a) We are certain of the following—

A competent immune system is essential for health.

Experimental lab studies demonstrate that certain synthetic chemicals affect the immune system (e.g., aromatic hydrocarbons; carbamates; heavy metals; organohalogens; organophosphates; organotin; oxidant air pollutants, such as ozone and nitrogen dioxide; and polycyclic aromatic hydrocarbons). These effects are manifested as alterations in the immune system that may lead to a decreased quality of life. These alterations include immune modulation expressed as an increase or decrease in measured immune parameters, hypersensitivity, and autoimmunity.

Changes in the characteristics of the immune system in humans and certain wildlife species have been associated with both therapeutic and environmental exposure to synthetic chemicals, e.g., diethylstilbestrol (DES), dioxin, polychlorinated biphenyls (PCBs).

Impairment of the immune system can result from alterations in the development of the immune system and may be long-lasting. The effects may not be manifested at hatching or birth and may not be expressed until the animal or human reaches adulthood.

Life-long capacity for immune response is determined early in development, during prenatal and early postnatal development in mammals and prehatching and early posthatching development in egg-laying species.

Alterations in the developing and mature immune systems may not be recognized as an adverse health effect until long after the exposure.

Some wildlife and human populations are exposed to elevated levels of certain synthetic chemicals.

The widespread exposure of populations of humans and wildlife to many man-made chemicals has made it difficult, if not impossible, to find control populations that have no exposure level. True control

populations for human and wildlife epidemiological studies are thus lacking.

b) We estimate with confidence that—

Certain synthetic chemicals, such as those listed above, released or reintroduced into the environment act upon the developing and mature immune systems in humans and other vertebrates.

Prenatal and early postnatal mammals and the immature and early life stages of amphibians, reptiles, fishes, and birds are likely to be the most vulnerable life stages to immunomodulation.

Vulnerability upon exposure varies among gender, species, and stages of the life cycle. In addition to embryos, fetuses, and the newborn, children, the very old, and certain populations (e.g., chronically ill, poorly nourished, HIV positive) are also likely to be more at risk.

In certain instances, humans and wildlife are experiencing immune alterations. Data suggest that immune alterations seen in wild animals and humans are consistent with those produced by synthetic chemicals identified as immunotoxic in studies with laboratory animals.

Immunotoxic effects expressed in individuals could therefore be expressed at the population level thus affecting biodiversity at the community or ecosystem level.

Immune system effects reported in wildlife, in parallel with *in vitro* and *in vivo* experimental studies, support the possibility for qualitative prediction of human effects.

Current predictive capability for immunomodulation is limited to identification of qualitative changes not quantitative changes.

c) Based on our current understanding we predict—

Certain synthetic chemicals can cause alterations of the developing immune system.

Alterations in immunologic function whether occurring prenatally or embryologically or later in life can translate into altered host resistance and susceptibility to disease, including autoimmune disease. Disease patterns are thus likely to be affected by immune modulation induced by immunological toxicants.

d) There are uncertainties in our understanding because—

More needs to be learned about how the immune system develops.

Few well-controlled human or wildlife ecoepidemiological studies that document immune modulation have been completed.

The lack of sensitive tests and the uncertainty about exposure have been impediments in many of these studies. Exposure is well known for some wildlife studies.

Information on exposure is limited. Little is known about the effects of long-term, low-level exposure.

Little is known about the effects of exposure to chemical mixtures. Most published studies use single agents when testing for the effects of environmental exposure. The specific components of environmental mixtures are rarely defined.

The pharmacokinetics of many immunotoxic compounds in target organs is understood in experimental animals but not in humans and wildlife.

Data are lacking about the persistence of the effects of immunomodulators.

For regulatory purposes, the current lack of knowledge about the mechanisms leading to immunomodulation makes cause-and-effect linkages extremely difficult.

Uncertainty exists about whether the right questions have been asked concerning the mechanisms of immune modulation.

e) Our judgment is that—

The potential exists for widespread immunotoxicity in humans and wildlife species because of the worldwide lack of appropriate protective standards. This is based on documented immune effects from high-level exposure, plus a large amount of anecdotal data on humans and wildlife, and strong experimental animal data.

Although exposure is widespread, it varies from region to region and individual to individual. Based on anecdotal information, it is presumed that exposure is greater in Eastern Europe and the former Soviet Union and especially in developing countries because of lack of adequate environmental regulations and enforcement.

The lack of human epidemiological studies in the developing world makes it impossible to determine the scale of immune modulation and/or autoimmune disease among these populations. The consequences of chemical exposure in developing countries may be severe because of multiple confounders such as poverty, malnutrition, and poor medical care. The consequences will be difficult to identify because of the lack of adequate control cohorts.

The risk of exposure to known immunomodulators is sufficient to warrant regulatory approaches that would limit exposure.

f) To improve our predictive capacity—

More basic research is needed on the development of the immune system of

diverse animal species and the factors that drive its maturation and senescence. Further study is needed to understand the mechanistic role of synthetic chemicals in the alteration of these processes.

Priority needs to be given to developing assays predictive of disease resistance for a variety of species. It is important to know how immune modulation affects increased prevalence of infectious diseases among humans and wildlife.

More emphasis must be placed on developmental immunotoxicology. This can be accomplished through collaborative research efforts to standardize protocols, share specimens, and to develop inexpensive, rapid, biomarkers of immunotoxicity. The use of the Internet and other online systems to apprise researchers of planned

and ongoing experiments will increase collaborative opportunities.

Models based on "real world" situations (dose, duration of exposure, timing) that include metabolism, pharmacokinetics, route of exposure, and target effects in a number of indicator species should be developed for extrapolation to humans and other species.

Ecoepidemiological criteria that include dose-response, time order (exposure precedes effect), specificity, strength of association, coherence, and predictability combined with laboratory validation are needed to improve the level of certainty in epidemiological studies.

More epidemiological research among susceptible populations, especially in developing countries, is needed.

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